270 00 120 KSP181
110 00 15
14/Ept &
Brochs
11-03-92
1 of 3

PATENT
1173-145P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	**Before the Board of Appeals**
Teizo Yoshimura et al	**Appeal No.:**
Serial No.: 07/330,446	**Art Unit: 1814**
Filed : March 30, 1989	**Examiner: Dian Cook**

For : HUMAN DERIVED MONOCYTE ATTRACTING PURIFIED PROTEIN PRODUCT USEFUL IN A METHOD OF TREATING INFECTION AND NEOPLASMS IN A HUMAN BODY, AND THE CLONING OF FULL LENGTH cDNA THEREOF

PATENT
1173-145P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	Before the Board of Appeals
Teizo Yoshimura et al	Appeal No.:
Serial No.: 07/330,446	Art Unit: 1814
Filed : March 30, 1989	Examiner: Dian Cook

For : HUMAN DERIVED MONOCYTE ATTRACTING PURIFIED PROTEIN PRODUCT USEFUL IN A METHOD OF TREATING INFECTION AND NEOPLASMS IN A HUMAN BODY, AND THE CLONING OF FULL LENGTH cDNA THEREOF

TABLE OF CONTENTS

PATENT
1173-145P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	Before the Board of Appeals
Teizo Yoshimura et al	Appeal No.:
Serial No.: 07/330,446	Art Unit: 1814
Filed : March 30, 1989	Examiner: Dian Cook

For : HUMAN DERIVED MONOCYTE ATTRACTING PURIFIED PROTEIN PRODUCT USEFUL IN A METHOD OF TREATING INFECTION AND NEOPLASMS IN A HUMAN BODY, AND THE CLONING OF FULL LENGTH cDNA THEREOF

A P P E A L B R I E F

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

October 13, 1992
(after Holiday)

Sir:

This Appeal Brief is respectfully submitted on behalf of the Appellants in connection with the above-identified application.

This is an appeal of the Examiner's Final Rejection dated February 10, 1992.

STATUS OF THE CLAIMS ON APPEAL

Claims 1-7, 9 and 11-25 are pending in the above-identified application with claims 9 and 11-19 on appeal, and claims 1-7 and 20-25 being withdrawn from consideration.

STATUS OF AMENDMENTS

Appellants filed a Proposed Amendment on June 10, 1992 under 37 C.F.R. 1.116 in response to the Final Rejection of February 10, 1992.

In the Examiner's subsequent Advisory Action of June 25, 1992, it was indicated upon filing of a Notice of Appeal, the Proposed Amendment of June 10, 1992 would be entered into the file, and the status of the claims would be that claims 9 and 11-19 remain rejected.

The Examiner's Advisory Action of June 25, 1992 further indicated that the Appellants' Response of June 10, 1992 overcame previous rejections of claims 10-11 under 35 U.S.C. §112, first and second paragraphs, as well as earlier rejections of claims 9-19 under 35 U.S.C. §103 over Ramb et al and Yoshimura et al.

SUMMARY OF THE INVENTION

The present invention pertains primarily to a cDNA encoding for a human monocyte chemoattractant peptide comprising the nucleotide sequence recited in claim 9 capable of encoding a polypeptide possessing monocyte chemoattractant activity. The invention is further concerned with providing a method of producing human monocyte chemoattractant factor which comprises culturing a microorganism having therein a vector containing a cDNA nucleotide sequence as recited in claim 9.

REFERENCES RELIED UPON IN THE FINAL REJECTION

The Examiner maintains a rejection of claims 9 and 11-19 under 35 U.S.C. §103 as being unpatentable over the following reference:

Valente, Anthony J. P. et al, Biochemistry, Volume 72, pages 4162-4168 (1988).

ISSUES ON APPEAL

The following issues are presented for appeal:

(1) Whether claim 9 is enabled and patentable under the provisions of 35 U.S.C. §112, first paragraph ?

(2) Whether claim 9 is patentable under 35 U.S.C. §112, second paragraph, in view of its use of the phrase "or a mutation or

variation thereof" when referring to the cDNA sequence recited ?

(3) Whether claims 9 and 11-19 are patentable under 35 U.S.C. §103 over the disclosure of the Valente et al reference of record?

GROUPING OF THE CLAIMS

Appellants' claims 9 and 11 relate to cDNA's encoding human monocyte chemoattractant peptides. These claims do not stand or fall together with the other pending on appeal claims, or with each other. In this regard, claim 11 clearly limits the polypeptide amino acid sequence of the monocyte chemoattractant peptides produced, while no such limitation exists in claim 9.

Claims 12-14 relate to vectors containing the cDNA recited in claim 9. These claims do not stand or fall together with the other claims pending on appeal, or with each other. In this respect, claim 13 recites that the vector is a plasmid, while no such limitation occurs in claim 12. Moreover, claim 14 recites that the vector is LAMBDA ZAP II. Accordingly, it is entirely possible that claims 13 and 14 may be found patentable by the Honorable Board, even if claim 12 is not found patentable. Similarly, the Honorable Board may find claim 14 patentable, even if claims 12 and 13 are found non-patentable.

Claims 15 and 16 relate to microorganisms containing vectors

which have therein the cDNA of claim 9. These claims do not stand or fall together with other claims pending on appeal, or with each other. In this regard, claim 16 depends from claim 13 which requires that the vector utilized be a plasmid. No such limitation occurs in claim 15.

Claim 17 recites an *E. Coli* microorganism containing a vector having therein the cDNA of claim 9. This claim does not stand or fall with other claims pending on appeal, due to a specific recitation of an *E. Coli* microorganism and the fact that its vector is a LAMBDA ZAP II vector.

Claims 18 and 19 recite a method of producing human monocyte chemoattractant factor. These claims do not stand or fall together with other claims pending on appeal, or with each other. For example, claim 19 particularly recites the *E. Coli* microorganism and vector found in claim 17, while claim 18 does not contain such a limitation.

Accordingly, it is submitted to the Honorable Board that the patentability of each of claims 9, 11, 12, 13, 14, 15, 16, 17, 18 and 19 must be adjudged separately by the Honorable Board of Appeals in its opinion in the matter of the present Appeal.

APPELLANTS' ARGUMENTS

(1) Whether claim 9 is enabled and patentable under the provisions of 37 C.F.R. §112, first paragraph ?

The Examiner has finally rejected claim 9 alleging non-enablement under 35 U.S.C. §112, stating in part as follows:

"...The disclosure is enabling only for claims limited to the sequence of a human monocyte chemoattractant peptide, as disclosed by applicants for reasons of record...This rejection is maintained from the previous Office Action. Claims ... are drawn to a "bio-equivalent" peptide which possesses a high degree of homology."

The above remarks of the Examiner were made before entry of the Appellants' Proposed Response of June 10, 1992. In the Proposed Response of June 10, 1992, the term "or a bioequivalent thereof which possesses a high degree of homology therewith" was deleted from claim 9, and the term "or a mutation or variation thereof" was inserted into claim 9, so that the above comments of the Examiner are now moot. Nonetheless, the Examiner's first Office Action dated May 15, 1991 contained a rejection of claim 9 for the use therein of the phrase "a mutation or variation" when referring to cDNAs. Specifically, the Examiner's first Office Action indicated as follows at page 6:

"Applicants have disclosed and enabled a particular sequence of a human monocyte chemoattractant peptide. To include variations of said peptide in the claims is beyond the scope of the invention as enabled in the specification."

Even in view of the above statements of the Examiner, it is submitted to the Honorable Board that claim 9 as presently amended is patentable and fully enabled under the provisions of 35 U.S.C. §112, first paragraph, since the statute requires nothing more than objective enablement, and whether this is achieved by the use of illustrative examples over a broad terminology is of no importance, In re Marzocchi et al, 439 F2d 220 169 USPQ 367 (CCPA 1971). Similarly, the Appellants are not required to recite a fixed number of nucleotide sequences in their specification to properly support claim 9, or required to provide multiple examples relating to the same, since such numbers necessarily must depend upon the circumstances of each particular case, In re Shokal et al, 242 F2d 771, 113 USPQ 283 (CCPA 1957). Further to the above, it is submitted to the Honorable Board that the following functional language occurring in claim 9 :

> "...which is capable of encoding a polypeptide possessing monocyte chemoattractant activity..."

clearly serves to limit the cDNAs encompassed by claim 9, such that the claim as presently pending, is fully enabled by Appellants' disclosure.

Furthermore, an assay which can be employed to assess the chemoattractant activity of any peptide to be tested for such activity is clearly set forth on page 27, line 23 through page 24, line 10 of the specification. Thus, inasmuch as a cDNA encoding or peptide having chemoattractnat activity is disclosed, methods of making variant nucelotide sequences are well known in the art of

recombinant DNA technology (e.g., J. Sambrook et al, "Molecular Cloning, A Laboratory Manual", 2nd Edition, Chapter 15, c. 1989 by by Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.), and a definite test of chemoattractant activity of peptides encoded by such variant cDNA sequences as might be produced is also disclosed, one of ordinary skill in this art would consider "mutations or variants thereof", in reference to the cDNA of claim 9, to be enabled by the disclosure of the present application.

Based upon the above considerations, withdrawal of the Examiner's rejection under 35 U.S.C. §112, first paragraph, of claim 9 is required.

(2) Whether claim 9 is patentable under 35 U.S.C. §112, second paragraph ?

The Examiner states at page 2 of the Final Office Action that claim 9 is :

> "Drawn to a biological equivalent of a monocyte chemoattractant protein which possesses a high degree of homology. It is uncertain what is intended by "high degree of homology", i.e., what level of homology is intended ?"

In the Appellants' Proposed Amendment of June 10, 1992, claim 9 was amended so that the term "high degree of homology" was deleted from the claim. Accordingly, the above grounds for rejecting claim 9 under 35 U.S.C. §112, second paragraph, has been overcome. Nonetheless, it is noted that in the Examiner's first Office Action at page 6, the Examiner rejected previous claim 10

for the use of the phrase "mutation or variation" therein, when referring to the cDNA sequence of claim 9, alleging the same phrase to be vague. More particularly, the Examiner stated as follows in his first Office Action:

> "[The] claim ... is drawn to a "mutation or variation" in the cDNA sequence, the meaning of which is vague. It is uncertain what this claim encompasses, i.e., does this mean additional DNA sequences, a truncated form of the sequence, a leader sequence or something else ? "

Even in view of the above statements by the Examiner, it is submitted that claim 9 is fully patentable under the provisions of 35 U.S.C. §112, second paragraph, since the functional language thereon "which is capable of encoding a polypeptide possessing monocyte chemoattractant activities" serves to render definite the various cDNA sequences encompassed by claim 9. In this respect, it is entirely acceptable to name an ingredient, reactant, or even a radical in terms of what it does rather than solely in terms of what it is, Ex parte Pontius et al, 169 USPQ 122 (POBA 1970), In re Fuetterer, 319 F2d 259 (CCAP 1963), In re Cohn, 438 F2d 989, 169 USPQ 95 (CCPA 1971), In re Barr et al, 444 F2d 588, 170 USPQ 330 (CCPA 1971).

Further to the above, it is submitted to the Honorable Board that since the Appellants' claim 9 is understandable and defines the subject matter which the Appellants regard as their invention, it must be adjudged to meet the requirements of 35 U.S.C. §112, second paragraph, In re Kamal et al, 398 F2d 867, 158 USPQ 320 (CCPA 1968).

Based upon the above considerations, a reversal of the Examiner's rejection of claim 9 under 35 U.S.C. §112, second paragraph is required.

(3) Whether claims 9 and 11-19 are patentable under 35 U.S.C. §103 over the disclosure of the Valente et al reference of record ?

In the Examiner's final Office Action at pages 3-4, he states as follows regarding his obviousness rejection of claims 9 and 11-19:

> "In addition, applicants have not adequately differentiated their protein from that described by ...Valente et al. Applicants argue that the protein is not the same as that described by Valente et al by pointing out that the molecular weights of the two proteins are different. This is not deemed to be persuasive ...In addition, the proteins described by ...Valente et al in the present application had the same molecular weight (approximately 15,0000 kD as measured by SDS-PAGE and all possess monocyte chemoattractant activity. Therefore, because applicants have not definitively differentiated their protein from those described by the prior art, the protein of the present application is deemed to be obvious in view of the prior art."

In response to the above assertion of the Examiner in his Final Office Action, the Appellants submit that biological fluids often contain many different chemotactic attractants, such as small peptides, different proteins and even non-protein molecules such as leucotrienes. Moreover, in some cases such attractants may be small lipids or peptides bound to a protein. Accordingly, it is submitted to the Honorable Board that simply because two different materials from biological fluids possess macrophage chemotactic

activity, this does not by itself provide a basis to conclude that such materials are obvious over each other under 35 U.S.C. §103. Similarly, it does not provide a basis for concluding that cDNA constructs for the production of such different materials would be obvious over each other under 35 U.S.C. §103.

Furthermore, in the cited Valente et al reference, it is reported that the purified protein having monocyte chemotactic activity had an estimated molecular mass of 14,500. This is different from the peptides produced by way of the Appellants' invention, which possess an estimated molecular mass of about 8,400 Daltons (see pages 4-5 of Appellants' specification), notwithstanding the Examiner's assertions to the contrary. Thus, it is submitted to the Honorable Board that the disclosure in the cited Valente et al reference of a polypeptide possessing a molecular weight much higher than Appellants', cannot render obvious the Appellants' presently claimed inventions. This is especially true, since the Valente et al reference does not report the sequence the peptide produced therein.

One reason the Examiner provides for maintaining his rejection of the claims over the Valente et al reference, is that

> "Appellants have not definitively differentiated their protein from those described by the prior art".

In reply to the above contention of the Examiner, it is submitted to the Board that since Valente et al never isolated a protein of 8,400 daltons molecular weight possessing monocyte chemoactivity. The present inventors have definitively

differentiated their protein from the prior art of Valente, which has a molecular weight of 14,500 daltons. Furthermore, the Declaration under 37 C.F.R. 1.132, filed with the Amendment under 37 C.F.R. 1.116 on June 10, 1992 clearly differentiates the amino acid composition of the chemoattractant peptide of the present invention from that disclosed in the Valente reference. The Board is asked to compare Table II of Yoshimura et al, J. Immunol., 142: 1956 (1989), (attached to said Declaration) with Table II of the Valente reference.

It is additionally submitted to the Honorable Board that the Examiner's rejection necessarily relies upon an obvious to try test of patentability which is not a valid test of patentability. In re Mercier, 515 F2d 1161, 185 USPQ 774 (CCPA 1975). Instead, the Examiner must determine the obviousness or non-obviousness of the inventors' claims based upon the subject matter claimed therein "as a whole", while examining the scope and content of the prior art, differences between the prior art and the claimed invention, the level or ordinary skill in the pertinent art and secondary considerations, such as commercial success, long felt need and non-obvious results, Graham v. John Deere, 383 US 1, 148 USPQ 459 (1966).

The Honorable Board is also reminded that an Examiner's holding of obviousness under 35 U.S.C. §103, even *prima facie* obviousness, is but a procedural mechanism to allocate in an orderly way the burdens of going forward and of persuasion between

the Examiner and an applicant. Thus, the present Examiner's holding of obviousness was dissipated when the Appellants produced their rebuttal evidence, regardless of whether the Board finds that the Examiner's initial case of obviousness was strong or weak. Accordingly, all of the above evidence and facts must be considered anew by the Honorable Board in determining whether the Examiner's rejection of the claims as obvious should be affirmed, In re Piasecki, 223 USPQ 785 (Fed. Cir. 1984).

Based upon the above considerations, the Honorable Board is respectfully requested to reverse the Examiner's outstanding rejection of the Appellants' claims 9 and 11-19 under 35 U.S.C. §103.

C O N C L U S I O N

Appellants' argument have distinctly pointed out the errors in the Examiner's rejections of claims 9 and 11-19 under 35 U.S.C. §112 and 35 U.S.C. §103. In consequence, it is submitted that the Examiner's rejection under such statutes are in error.

The Honorable Board of Appeals is therefore respectfully requested to reverse the Examiner's final rejection of claims 9 and 11-19 and to render a decision favorable to the appellants.

The required Appeal Brief fee in the amount of $270.00 is enclosed herewith.

Pursuant to 37 C.F.R. 1.17 and 1.136(a), the Appellants re-

spectfully petition for a one (1) month extension of time for filing a response in connection with the present application and the required fee of $110.00 is attached hereto.

Please charge any fees or credit any overpayment pursuant to 37 C.F.R. 1.16 or 1.17 to Deposit Account Number 02-2448.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH

By: _____ #33,805
Gerald M. Murphy, Jr.
Reg.No. 28,977
POB 747
301 North Washington Street
Falls Church, Virginia 22040-0747

703/241-1300
GMM/JWB:bmp
(1173-145P, SN 07/330,446)
Enclosure

A P P E N D I X

Claim 9. A cDNA encoding for a human monocyte chemoattractant peptide, which comprises the following nucleotide sequence, or a mutation or variation thereof, which is capable of encoding a polypeptide possessing monocyte chemoattractant activity:

CAG CCA GAT GCA ATC AAT GCC CCA GTC ACC TGC TGT TAT AAC
TTC ACC AAT AGG AAG ATC TCA GTG CAG AGG CTC GCG AGC TAT
AGA AGA ATC ACC AGC AAG TGT CCC AAA GAA GCT GTG ATC TTC
AAG ACC ATT GTG GCC AAG GAG ATC TGT GCT GAC CCC AAG CAG
AAG TGG GTT CAG GAT TCC ATG CAG CAC CTG GAC AAG CAA ACC
CAA

wherein,

C is cytosine, T is thymine, A is adenine, and G is guanine.

Claim 11. The cDNA coding of claim 9, wherein said nucleotide sequence codes for a polypeptide comprising the following amino acid sequence and possessing monocyte chemoattractant activity:

Gln Pro Asp Ala Ile Asn Ala Pro Val Thr Cys Cys Tyr Asn Phe

Thr Asn Arg Lys Ile Ser Val Gln Arg Leu Ala Ser Tyr Arg Arg

Ile Thr Ser Ser Lys Cys Pro Lys Glu Ala Val Ile Phe Lys Thr

Ile Val Ala Lys Glu Ile Cys Ala Asp Pro Lys Gln

wherein,

Met is methionine,
Lys is lysine,
Val is valine,
Ala is alanine,
Leu is leucine,
Cys is cysteine,
Ile is isoleucine,
Gly is glycine,
Asp is aspartic acid,
Asn is asparagine,
Tyr is tyrosine,
Glu is glutamic acid,
Trp is tryptophan,
His is histidine,

Thr is threonine, Pro is proline,
Phe is phenylalanine, and Gln is glutamine.

Claim 12. A recombinant vector containing the cDNA of claim 9.

Claim 13. The vector of claim 12 which is a plasmid.

Claim 14. The vector of claim 13, which is derived from LAMBDA ZAP II.

Claim 15. A microorganism containing the vector of claim 12.

Claim 16. A microorganism containing the vector of claim 13.

Claim 17. An *E. Coli* microorganism containing the vector of claim 14.

Claim 18. A method of producing a human monocyte chemoattractant factor which comprises culturing the microorganism of claim 16, under conditions that allow for expression of said factor.

Claim 19. A method of producing a human monocyte chemoattractant factor which comprises culturing the microorganism of claim 17, under conditions that allow for expression of said factor.